The Cost of Adverse Drug Events in Ambulatory Care

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ABSTRACT

Background: Many justifications for ePrescribing predict savings achieved by reducing the number of adverse drug events (ADEs) in the ambulatory setting; however, there is little evidence from which to estimate the size of these savings. Estimating the cost of ADEs in the ambulatory setting would improve the reliability of these predictions.

Methods: We identified patients with potential ADEs in a primary care practice setting and characterized the patient’s age along with charge and utilization indicators for 6 weeks pre- and post-event. We then used linear regression to determine charges attributable to an ADE.

Results: Charges were higher for patients following an ambulatory visit who were determined to have ADEs. This occurred in a linear fashion: 2 ADEs ($4,976); 1 ADE ($2,337); and no ADEs ($1,943). The charge attributable to a single ADE is $643 (2001 US dollars) or $926 (cost adjusted to 2006 US dollars).

Conclusions: Patients with ADEs incur greater charges. The charges attributable to an ambulatory ADE are a significant cost to the health care delivery system on the order of $8 billion annually.

INTRODUCTION

One of the major financial justifications for implementing outpatient computerized physician order entry (CPOE) or ePrescribing is the expected reduction in the number of adverse drug events (ADEs) but there is little data about the costs attributable to ADEs in the ambulatory setting or whether CPOE reduces the number of events.

Adverse drug events, defined as an injury resulting from an intervention related to medication use, and their associated costs have been studied extensively in the inpatient setting.1,2,3,4,5,6,7,8,9,10 These events have been shown to increase cost by $3,244 per adverse drug event.4 Much less is known about adverse drug events in the outpatient setting. Several studies have reported rates of adverse drug event rates as between 3% and 35% annually.11,12,13,14,15 A 1994 meta-analysis reported that 4.7% of hospital admissions (over one million) were the result of adverse drug events.16 Even less is known about the cost of adverse drug events in this setting. Most of the figures come from models and simulations rather than direct measurement.17,18,19

One retrospective cohort study among elderly adults in an ambulatory setting measured an increase in cost after an adverse drug event at $1,310 for all ADEs and $1,983 for preventable ADEs.20 The Center for Information Technology Leadership (CITL) estimated that eliminating 2.1 of our three million annual preventable ADEs (out of an estimated 8.8 million) that occur in the ambulatory setting annually in the U.S. would save $20 to $44 billion annually.21

In order to measure charges associated with adverse drug events in the ambulatory setting, we examined charges in patients with and without ADEs.

METHODS

Setting and Subjects:

We conducted the study, which was approved by the IUPUI IRB, at six primary care practices from IU Medical Group- Primary Care, a large practice affiliated with Indiana University School of Medicine. The physicians at all six practices used the Medical Gopher electronic medical record system,22 which is part of the Regenstrief Medical Record System (RMRS).23 The Medical Gopher provides CPOE with advanced decision support, workflow, organization, documentation, and communication functions. Patients eligible for inclusion in this study were 18 years of age or older and had at least one visit to one of the participating primary care practices during the study period.

Study Design:
The study was a retrospective cohort study nested within a randomized controlled trial (RCT) of ambulatory computer provider order entry comparing
adverse drug events, medical errors, and preventable adverse drug events. The RCT was a pre-post design with all patients aged 18 year or older who presented for care to one of the study practices during a six month period from January 2001 through June 2001 and were placed on a drug included in the detection criteria described below.

**Identification of Adverse Drug Events:**
The system and methods used to determine the incidence of adverse drug events are based on studies previously conducted at the Regenstrief Institute and Brigham and Women’s Hospital. Briefly, an expert panel, using rules derived from these previous studies, developed 122 criteria (available from the authors) to use as queries against the RMRS to select patients with potential adverse drug events. The criteria included drug-drug, drug-allergy, drug-lab value, drug-diagnosis, and drug-demographic (i.e. age) matches for adverse drug event detection. These candidate adverse drug events were then screened for duplicates, which were then removed. Finally, all candidate ADEs were reviewed to determine whether or not they were, in fact, an ADE. Controls were selected through an identical process except that, when the candidate ADE was reviewed, it was determined not be an ADE.

**Data Management:**
In addition to age and co-morbidities, we extracted inpatient and outpatient charges, number of medications, and total number of orders from the RMRS for a six week period before and after the trigger event. These variables and time interval were chosen a-priori based on previously reported methodology and analysis of costs attributable to ADEs.

Health care charges were determined using previously described methods. Briefly, the charges are derived from an internal costing system for a publicly supported county health care system that is part of the RMRS. We retrieved these charges from the RMRS for the period six weeks pre- and post-event for both inpatient and outpatient settings for aspects of care except non-procedural professional fees and sub-totaled them by revenue center. All charges were adjusted to 2001 U.S. Dollars using the inflation rates per annum published by the U.S. National Center for Health Statistics and U.S. Census Bureau.

**Charlson co-morbidity index calculation:**
The Charlson co-morbidity index is a method for classifying co-morbid conditions that predicts the risk of mortality. It is a weighted index that takes into account the number and the seriousness of co-morbid disease and includes inpatient and outpatient diagnoses for three years prior to the index date.

**Statistical Analysis:**
We imported this data into Excel® and SAS® for analysis. We calculated mean charges (outpatient, inpatient and total), age, number of medications, total orders, and Charlson co-morbidity index separately for all patients and grouped them by the number of ADEs the patient experienced during the study period. We also used linear regression (least squares) to model the log of the charges after the ADEs as a function of the number of ADEs, while controlling for covariates including the log of the charges after the ADEs, age, number of active medications, Charlson co-morbidity index, and total number of orders.

**RESULTS**
There were 866 patients who met the inclusion criteria of which we determined that 165 had experienced an ADE.

Average costs for six weeks before and after the encounter associated with the adverse drug event signal stratified by the number of adverse drug events are shown in Table 1.

**Table 1.** Average Cost (2001 dollars) of Pre and Post event Care for Patients by Number of ADEs

<table>
<thead>
<tr>
<th>ADEs (patients)</th>
<th>Pre-event (6 weeks)</th>
<th>Post-event (6 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (701)</td>
<td>$1,159</td>
<td>$1,943</td>
</tr>
<tr>
<td>1 (114)</td>
<td>$1,887</td>
<td>$2,337</td>
</tr>
<tr>
<td>2 (51)</td>
<td>$4,122</td>
<td>$4,976</td>
</tr>
</tbody>
</table>

Table 2 summarizes the characteristics of the patients stratified by the number of ADEs they experienced.

**Table 2.** Mean age, medications, Charlson co-morbidity index (CCI) and total orders for the 6 weeks prior to trigger event by number of ADEs

<table>
<thead>
<tr>
<th>ADEs</th>
<th>Age</th>
<th>Meds</th>
<th>CCI</th>
<th>Orders</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>53</td>
<td>5.6</td>
<td>1.75</td>
<td>10</td>
</tr>
<tr>
<td>1</td>
<td>56</td>
<td>6.5</td>
<td>2.52</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>9.9</td>
<td>4.62</td>
<td>38</td>
</tr>
</tbody>
</table>

The ANOVA analysis demonstrated the following ADE charge relationship (p<0.0001): $\text{charges after} = e^{(4.57+0.234\log(\text{charges before})+0.005\times\text{ADE})}$

The charge difference after an encounter increased by 1.82 times for every occurrence of an ADE.
For our population, the average incremental charge with one ADE is equal to $643 in 2001 US dollars or $926 in inflated 2006 U.S. dollars. Controlling for the additional covariates: age, medications, Charlson co-morbidity index, and total orders, did not change the result significantly (p<0.0001).

**DISCUSSION**

This study demonstrates that total charges were approximately $926 higher for patients that experience ADEs in the ambulatory setting than those that did not have an ADE.

Our estimate is similar in magnitude to those Field, et al reported - $926 versus $1,396 (adjusted to 2006 U.S. dollars). We believe there are several notable reasons for the disparity. First, Field’s population was exclusively a Medicare population over 65 yrs of age (46% 75-84) while our population is from a General Internal Medicine population of 18 yrs and older (mean age 54). Age was identified as a covariate with a positive correlation for charges in both studies. Second, Field’s paper presumably includes charges for professional services which we did not include. Third, Field’s study used a variety of methods to identify ADEs based on available data but they were not verified as ADEs. Additionally, our charges are derived from an internal costing system at a publicly supported county health care system and may actually under represent charges in a more representative health care delivery system. Finally, the comparison (no ADE) group in our study is more comparable to those patients who experienced ADEs than in the Field’s study. They were matched based on receiving the same medications, experiencing the same event that indicated a potential ADE, being cared for in the same practice and they represent a much sicker population as evidenced by more medications and higher Charlson co-morbidity indices.

Using the CITL estimate of 8.8 million ambulatory ADEs per year, our data suggests that these cost our health care system $8.1 billion dollars annually, with nearly $3 billion of that in preventable events. Or, to put it in more direct perspective, an average physician seeing 2,500 patients during a year could prevent nine ADEs on average based on the CITL model and confirmed in our study (9.3 ADEs). This would save $8,334 per year per provider each year.

Additionally, our study highlights the higher charges for care for sicker patients. The number of medications dispensed, the Charlson co-morbidity index, the number of orders, and total charges for care prior to the trigger event clearly suggest that patients who experienced an ADE were sicker and more costly than those who do not even before the event. Previous studies have demonstrated that both the Charlson co-morbidity index and the number of prescribed medications have strong predictive validity for health care utilization and cost. We found that the cost of an ADE is relative (1.8 times) to the incremental costs subsequent to an encounter and these costs are higher in sicker patients.

There are several limitations of this study. First, the data come from patients cared for in a single, multi-site, academically affiliated primary care practice in an urban setting which may somewhat limit the generalizability of the results. Second, we were only able to measure charges and not costs. Also, we did not measure indirect costs such as lost productivity so we may substantially underestimate the total costs.

In order to evaluate health information technologies, we need good estimates of their value which requires credible information about the nature of the problem, as well as benefits obtained. Credible information about the costs of ADEs in the ambulatory setting, combined with data about the potential for ambulatory CPOE with clinical decision support to reduce ADEs, will improve our understanding of the benefits it can provide.

**Acknowledgements:** This work was performed at the Regenstrief Institute Inc., Indianapolis, IN. It was supported in part by: grant T15 LM07117 from the National Library of Medicine; and grant U18 HS11169 from the Agency for Healthcare Research and Quality.

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